Bevacizumab Maintenance in Patients with Advanced Non–Small-Cell Lung Cancer, Clinical Patterns, and Outcomes in the Eastern Cooperative Oncology Group 4599 Study

Results of An Exploratory Analysis

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Introduction: The Eastern Cooperative Oncology Group (ECOG) 4599 study showed a significant survival benefit with the use of bevacizumab (BV) in combination with carboplatin and paclitaxel (CP) in comparison with CP chemotherapy alone in patients with previously untreated advanced, metastatic or recurrent non–small-cell lung cancer (NSCLC). Such results were achieved using BV as maintenance therapy until progressive disease. Because current data on single-agent BV maintenance in non–small-cell lung cancer are limited, we present a retrospective analysis of safety and efficacy outcomes for patients who received maintenance BV after induction treatment and the maintenance-eligible population of the control arm in ECOG 4599.

Methods: Landmark analyses were conducted in patients in both the CP and CP+BV groups who were alive and progression free through the completion of six cycles + 21 days. The BV maintenance population consisted of patients in the CP+BV arm, who were alive without progressive disease before the start of maintenance (maintenance-nonprogressor population). CP nonprogressors were those patients in the CP-alone arm without progressive disease after six cycles of CP + 21 days.

Results: Two hundred and seventeen patients (51%) were alive, progression free, and eligible for maintenance therapy six cycles + 21 days after induction CP+ BV compared with 134 patients (30%) in the CP-alone arm. Postinduction progression-free survival was significantly longer in the BV maintenance group relative to CP nonprogressors (4.4 versus 2.8 months; hazards ratio [HR] 0.64; $p < 0.001$). One-year overall survival rates were 75% for the BV maintenance group versus 69% in the CP nonprogressor group. Two-year overall survival rates were 34% for the BV maintenance group versus 25% in the CP nonprogressor group. Median postinduction overall survival (OS) was also significantly longer for the BV-maintenance group compared with CP nonprogressors (12.8 versus 11.4 months; HR 0.75; $p = 0.030$). Within the subgroup having complete response or partial response after induction, the progression-free survival and OS hazard ratio estimates were 0.59 (95% [confidence interval] CI: 0.41–0.84) and 0.78 (95% CI: 0.53–1.14), respectively. In the maintenance setting, BV was associated with a less-than 1% rate of grade 3 or 4 hematological toxicities, no grade 3 or 4 nausea, vomiting or diarrhea, and no grade 5 toxicities.

Conclusions: In this retrospective analysis of patients in the ECOG 4599 study, who were alive, progression free, and on-study 21 days after six cycles of induction therapy, significant reductions in HRs for progression (0.64, $p < 0.001$) and survival (0.75, $p = 0.03$) were associated with BV treatment during induction and maintenance compared with CP induction therapy alone and suggestive of possible benefit because of bevacizumab maintenance.

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Lung cancer is the leading cause of cancer-related death in the United States and worldwide.[1] Although modest progress has been made with the use of chemotherapy in patients with metastatic lung cancer, additional treatment options are needed. Given the preponderant role it plays in tumor growth and development, angiogenesis has become an important therapeutic target in lung cancer.[2,3] Bevacizumab (BV; Avastin, Genentech, South San Francisco, CA) is a recombinant, humanized monoclonal antibody against vascular endothelial growth factor (VEGF), a critical factor in tumor angiogenesis.[4] The Eastern Cooperative Oncology Group (ECOG) 4599 study, a phase III randomized controlled trial, compared the efficacy and safety of the use of carboplatin and paclitaxel (CP) alone or in combination with BV in patients with nonsquamous cell, stage IIIB to IV non–small-cell lung cancer (NSCLC).[5] Median progression-free survival (PFS) was significantly improved in the CP+BV arm (6.2 versus 4.5 months; hazard ratio [HR] = 0.66;

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$p < 0.0001$) and median overall survival (OS), the primary endpoint, was also significantly increased in the CP+BV arm (12.3 versus 10.3 months; HR = 0.79; $p = 0.003$).The results of this trial led to the Food and Drug Administration approval of CP+BV for the treatment of patients with stage IIIB/IV nonsquamous NSCLC.

In the ECOG 4599 study, the significant survival benefits observed in the CP+BV arm were achieved using BV both during induction and as maintenance therapy until progressive disease (PD). However, real-world data show divergent patterns of BV use as maintenance therapy subsequent to CP+BV induction even though its antiangiogenic mechanism of action supports its continued use until PD.[2] In addition, in preclinical cancer models continuous VEGF suppression with BV has been shown to be key to tumor control.[6–8] Furthermore, data from the GOG-218 trial, a randomized, double-blind, placebo-controlled phase 3 trial of CP with or without BV in patients with stages III or IV ovarian cancer, strongly suggests that maintenance BV is associated with a significant improvement in PFS in this patient population.[9] Because current data on single-agent BV maintenance in NSCLC are limited, we present a retrospective analysis of safety and efficacy outcomes for patients who received maintenance BV after induction treatment and the maintenance-eligible population of the control arm in ECOG 4599.

PATIENTS AND METHODS

ECOG 4599 Patients and Study Design

Full details of patient eligibility and clinical trial design for the ECOG 4599 trial have been previously described.[5]In brief, between July 2001 and April 2004, chemotherapy naïve patients with recurrent or advanced NSCLC (stage IIIB or IV) were randomized to CP chemotherapy alone or in combination with BV. Other inclusion criteria included measurable disease, ECOG performance status (PS) of 0 or 1, and adequate hematologic, hepatic, and renal function. Patients with squamous cell histology, hemoptysis, or central nervous system metastases were excluded.

Randomized patients were stratified by the presence of measurable disease, prior radiotherapy, percentage weight loss (< 5%, ≥ 5%), and disease stage (IIIB not recurrent, IV not recurrent, and IV recurrent). Patients were randomly assigned to one of two treatment arms: (1) C (area under the curve = 6 mg/mL, day 1), P (200 mg/m^2, day 1), and BV (15 mg/kg, day 1), or (2) treatment with CP alone. Treatment cycles were repeated every 3 weeks, and tumor assessments were performed every 6 weeks for 24 weeks, then every 9 weeks for the remainder of the treatment period, and then every 12 weeks after the completion of treatment. Patients in the CP cohort stopped chemotherapy after six cycles. Patients on CP+BV stopped chemotherapy after six cycles and continued on BV maintenance until disease progression. All tumor responses were determined using Random Evaluation Criteria In Solid Tumors, and toxicity was graded using the National Cancer Institute Common Terminology Criteria, version 2.0 (Cancer Therapy evaluation Program, April 30, 1999). The primary endpoint of the study was OS.

ECOG 4599 Maintenance BV Retrospective Statistical Analysis

Landmark analyses were conducted in patients in both the CP and CP+BV groups, who were alive and progression free through the completion of six cycles + 21 days. The landmark date was chosen to approximate the end of the induction period for both patient groups and the beginning of the seventh cycle of therapy for patients receiving BV maintenance. The BV-maintenance population consisted of patients in the CP+BV arm without PD before the start of maintenance (maintenance-nonprogressor population). CP nonprogressors were those patients in the CP-alone arm without PD after six cycles of CP + 21 days.

Measuring PFS and OS from the landmark date rather than from the date of randomization eliminates the potential for lead-time bias that could be caused by variations in the timing of cycles among different patients. Response rates, PFS, OS, and 1-year survival rates were estimated using Kaplan–Meier methods. HRs were based on a Cox model that adjusted for baseline factors including age, sex, race, ECOG PS, stage of disease, weight loss, disease histology, and best response to induction therapy.

RESULTS

Patient Disposition and Demographics

Between July 2001 and April 2004, 869 patients were randomized to treatment (Fig. 1). Among the 440 patients randomized to CP, 194 (44%) completed six cycles of induction therapy and 134 (30%) were alive and progression free at the landmark date. Among the 429 patients randomized to CP+BV, 258 (60%) completed six cycles of induction therapy and 217 (51%) were alive and progression free at the landmark date. Patient and disease characteristics were generally similar for the CP nonprogressor and BV-maintenance populations (Table 1). There was, however, a significantly ($p = 0.003$) larger proportion of patients whose best response through induction therapy was a complete response or partial response in the BV-maintenance group relative to patients in the CP group (57% versus 40%, respectively). Baseline factors significantly associated with a higher likelihood of completing six cycles of induction therapy and being alive and progression free at the landmark date were induction treatment with CP+BV rather than CP, ECOG PS 0 rather than 1, weight loss less than 5%, and adenocarcinoma histology.

Duration of Treatment and Safety

Among the 217 patients in the BV maintenance group, 95%, 75%, 50%, and 25% completed 7 or more, 9 or more, 12 or more, and 16 or more cycles of therapy from the start of induction, respectively. Ten of 217 patients (5%) who were eligible to receive BV maintenance treatment did not do so but were included in this analysis (intention-to-treat). The main reasons for BV discontinuation during maintenance were PD (70%) and toxicity (10%). Treatment-related grade 3 to 5 adverse events (AEs) occurred more commonly during induction than postinduction, with generally lower incidence rates of grade 3 or 4 AEs during BV maintenance than during

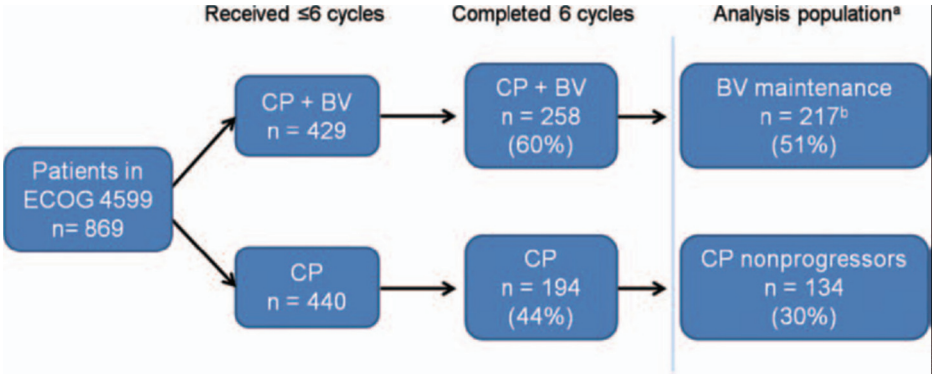

FIGURE 1. ECOG 4599 patient disposition and analysis population. *A*, Analyzable patients: alive and without PD through six cycles + 21 days; (*B*, a total of 207 patients completed at least seven cycles of BV treatment. BV, bevacizumab; CP carboplatin + paclitaxel; PD, progressive disease.

TABLE 1. Patient and Disease Characteristics at Baseline for the Analysis Population by Treatment Group

Characteristic, n (%)	CP Nonprogressors (n = 134)	BV Maintenance (n = 217)	Analysis Population (n = 351)	p^a
Age <70 yrs	102 (76)	165 (76)	267 (76)	0.986
Female sex	62 (46)	107 (49)	169 (48)	0.580
White, race	122 (91)	183 (84)	305 (87)	0.070
ECOG PS 0 vs. 1	69 (51)	97 (45)	166 (47)	0.216
Stage IIIB vs. IV	16 (12)	33 (15)	49 (14)	0.391
Weight loss <5%	105 (78)	175 (81)	280 (80)	0.604
Adenocarcinoma	99 (74)	161 (74)	260 (74)	0.948
Best induction response				
CR/PR	54 (40)	123 (57)	177 (50)	0.003
SD	51 (38)	64 (29)	115 (33)	0.097
Unknown	29 (22)	30 (14)	59 (17)	—

[a]Pearson test value for CP nonprogressor vs. BV-maintenance groups.
BV, bevacizumab; CP, carboplatin + paclitaxel; CR, complete response; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PR, partial response; SD, stable disease.

CP+BV induction, and the spectrum of toxicities differing between these groups (Table 2).

Because only patients alive and progression free 21 days after completing six cycles of therapy were included in this analysis, there were no grade 5 toxicities during induction for either treatment group. Rates of treatment-related toxicities do not represent those seen in the full ECOG 4599 study population and are generally more favorable.

Efficacy

Efficacy outcomes for patients in the CP nonprogressor and BV-maintenance groups are presented in Table 3. One hundred and sixty-two of 217 patients (75%) in the BV-maintenance group and 92 of 134 patients (69%) in the CP nonprogressor group were alive and on-study 1 year after the start of induction therapy. The 1-year PFS (32% versus 17%) and 2-year OS (34% versus 25%) rates were also higher for the BV-maintenance population compared with CP nonprogressors.

The Kaplan–Meier PFS and OS curves shown in Figure 2 estimate only postinduction survival for the subset of ECOG 4599 patients who were alive and progression free 21 days after six cycles of induction therapy. Postinduction PFS was significantly longer in the BV-maintenance group relative to CP nonprogressors (4.4 versus 2.8 months; HR 0.64; $p < 0.001$). Median postinduction OS was also significantly longer for the BV-maintenance group compared with CP nonprogressors (12.8 versus 11.4 months; HR 0.75; $p = 0.030$).

Median OS from start of induction was longer for the BV-maintenance group as compared with the CP nonprogressors (17.0 versus 15.8 months). Within the subgroup having complete response or partial response, the PFS and OS hazard ratio estimates were 0.59 (95% CI: 0.41–0.84) and 0.78 (95% CI: 0.53–1.14), respectively. The sample size for patients having stable disease after induction was considered too limited to reliably estimate hazard ratios for this population.

TABLE 2. Summary of Grade 3–5 Adverse Events of Interest in ECOG 4599 by Treatment Group

	Induction Therapy[a]		Postinduction Therapy
	CP (n = 134)	CP + BV (n = 217)	BV[b] (n = 217)
Treatment-Related AE, %	**Grade 3/4/5**	**Grade 3/4/5**	**Grade 3/4/5**
Any	22.4/15.7/0	22.1/34.6/0	13.8/5.5/1.8
Febrile neutropenia	2.2/0/0	5.5/0/0	0.5/0/0
Infection with Gr 3 or 4 neutropenia	0.7/0/0	1.8/0.9/0	0.9/0/0
Sensory neuropathy	9.0/0/0	8.3/0.5/0	2.3/0/0
Motor neuropathy	0.7/0/0	0.9/0/0	1.4/0/0
Nausea	3.0/0/0	4.1/0/0	0/0/0
Diarrhea	0.7/0/0	1.8/0.5/0	0/0/0
Vomiting	3.0/0/0	3.2/0/0	0/0/0
Fatigue	6.0/0.7/NA[c]	6.5/0/NA[c]	3.2/0/NA[c]
Cardiovascular (arrhythmia)	0/0/0	0/0/0	0/0.5/0.5
Cardiac ischemia	0/0/0	0/0/0	0/0/0.5
Hypertension	0/0/0	4.6/0/0	1.8/0.5/0
Thrombosis/embolism	0/0/0	0.5/0/0	0.9/0.9/0
Dyspnea	0.7/0/0	3.2/0.5/0	0.5/0/0
Proteinuria	0/0/0	0.5/0/0	2.8/0.5/0
Hemorrhage, any toxicity	0/0/0	0.9/0/0	0.5/0.5/0.9

[a]Through 6 cycles only.
[b]AEs for patients in the BV postinduction group are reported for patients receiving ≥7 cycles (n = 207).
[c]Not an option under CTCAE v3.0.
AE, adverse event; BV, bevacizumab; CP, carboplatin and paclitaxel.

DISCUSSION

In NSCLC, the significant survival benefits observed with BV+CP in the pivotal trial ECOG 4599 were achieved using BV therapy until PD.[5] However, the overall effects of maintenance BV therapy have not been previously evaluated. In this retrospective analysis of patients in the ECOG 4599 study, who were alive, progression free, and on-study 21 days after six cycles of induction therapy, significant reductions in hazard ratios for progression (0.64, $p < 0.001$) and survival (0.75, $p = 0.03$), suggestive of possible benefit because of BV maintenance were observed. Furthermore, at 1 and 2 years, 75% and 34%, respectively, of patients in the BV-maintenance group were alive versus 69% and 25% respectively, in the CP group. It is also important to view these survival rates in the context of the larger number of patients who were alive and progression free by the sixth cycle + 21-day time point in the BV+CP group compared with the CP group alone (51% versus 30%, respectively). This suggests superiority of the BV+CP regimen in allowing patients to receive and potentially benefit from maintenance therapy at the end of the induction phase.

These results are consistent with a recent retrospective analysis of the ARIES observational cohort study showing a potential benefit, in both OS and PFS, associated with maintenance BV beyond induction with first-line BV+CT.[10] In this trial, out of 1967 patients enrolled, 1215 (62%) were alive and progression free beyond their induction therapy. As measured from the initiation of BV+CP induction, median OS was 19.8 months for the BV-maintenance group versus 15.3 months in the control arm, and median PFS was 9.2 versus 7.9 months, respectively. Postinduction median OS was 15.7 months for the BV-maintenance group (n = 539; 95% CI 14.3–17.6; HR 0.71) versus 11.2 months (n = 674; 95% CI 10.1–12.5) for the control arm, and median PFS was 5.1 versus 3.8 months (HR = 0.77), respectively, also suggesting the potential benefit of BV maintenance in improving PFS and OS after treatment with induction BV+CP. Furthermore, data from this retrospective analysis of the ECOG 4599 are also consistent with results from the ATLAS trial, which investigated the use of BV ± erlotinib maintenance until disease progression in a selected nonprogressor population that received a BV-containing induction regimen.[11–13] This was a phase IIIb, randomized, controlled multicenter trial conducted in patients with locally advanced, recurrent, or metastatic NSCLC. ATLAS was stopped early after a preplanned interim efficacy analysis because the primary endpoint of improved PFS had been met with a median of 4.8 months for the BV+erlotinib arm versus 3.7 months for BV alone (HR = 0.71; $p = 0.0006$) as measured from the initiation of maintenance therapy. However, there was no difference in OS survival between the two arms (14.4 versus 13.3 months, respectively; HR = 0.92; $p = 0.57$)(Fig. 3).[13,14]

In addition, results from this retrospective analysis highlight that BV has a predictable and manageable safety profile in patients with NSCLC, both in combination with first-line chemotherapy and when continued as maintenance therapy in patients without PD. As observed in Table 2, in the maintenance setting, BV was associated with a less-than 1% rate of grade 3 or 4 hematological toxicities, no grade 3 or 4 nausea, vomiting or diarrhea, and no grade 5 toxicities. Furthermore, the safety and tolerability of BV

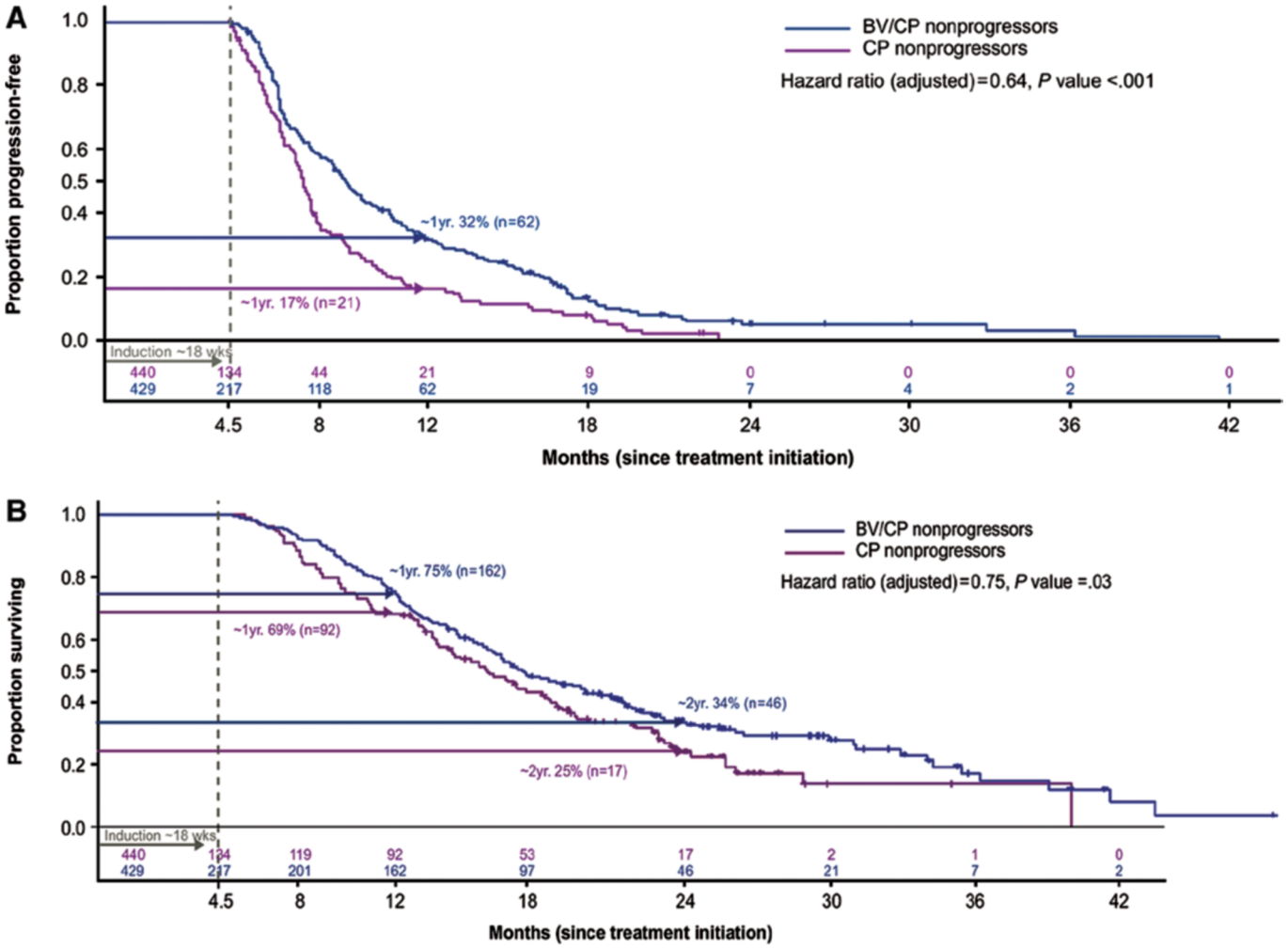

FIGURE 2. Kaplan–Meier estimates of (*A*) postinduction progression-free survival and (*B*) overall survival. Arrows indicate rates for patients at 1 year and at 2 years from the start of induction treatment (induction + postinduction periods). Numbers of patients at risk at designated time intervals are shown in this figure.

in the maintenance setting have been also highlighted in a recent analysis of SAIL, an international, multicenter, single-arm trial investigating the safety of first-line bevacizumab in combination with standard chemotherapy in advanced NSCLC. In this trial, a low incidence of grade 3 or worse AEs was reported with the use of maintenance BV and the most-common AEs were grade 1 to 2 epistaxis, hypertension, and proteinuria. Of particular note is that in this trial, the median time to progression was 8.9 months, and median OS was 18.8 months for patients who received BV maintenance as measured from the initiation of induction BV+CP.[15,16]

Even though BV has not been formally studied as a single agent in patients with metastatic NSCLC, preclinical models have shown that inhibition of the VEGF signaling causes robust and early changes in endothelial cells, pericytes, and basement membrane of vessels such as loss of endothelial fenestrations, suppression of vascular sprouting, and ceasing of patency and blood flow in some vessels.[6,17,18] In addition, in preclinical lung cancer models and in clinical settings, such as colorectal and ovarian cancers, continuous VEGF suppression with BV has been shown to be important for tumor control and survival.[6–9] Given that no tumor responses are observed with the use of single-agent BV, its benefit in the maintenance setting may be associated with a tumor static effect mediated by its antiangiogenic properties.

The limitations of this analysis are its retrospective nature and that E4599 was not designed to address the role of maintenance bevacizumab in this setting. The primary objective of ECOG 4599 was to evaluate the efficacy of induction BV+CP with maintenance BV upon disease progression in comparison with standard-of-care CP alone. That said, these results suggest that BV maintenance is an important component of the regimen used in ECOG 4599 and that its use is associated with a beneficial effect in PFS and OS in patients that received induction BV+CP and that did not progress after six cycles of therapy. This concept is supported by the PFS and OS rates at 1 and 2 years and the overall larger number of patients who can achieve these milestones compared with the CP arm.

In summary, the addition of BV to a standard, platinum-based, two-agent chemotherapy regimen confers a significant improvement on OS, PFS, and response rate in patients with nonsquamous, non–small-cell carcinoma, and such an improvement was achieved using BV therapy until PD. In this retrospective analysis of patients in the ECOG 4599 study we found significant reductions in hazard ratios for progression and survival associated with maintenance BV treatment in patients who were alive, progression free, and on-study 21 days after six cycles of induction therapy. These findings support the use of BV maintenance until disease progression as originally described in the landmark ECOG 4599 study.

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